REMARKS

In the Office Action dated September 25, claims 1-17 and 22-71 were rejected. The Examiner made the rejection non-final. In response, Applicant has not amended any of the clams, but submits the following comments. Reconsideration of this application is requested in view of the following remarks.

In the Office Action, claims 1-17 and 22-71 stand rejected under the judicially-created doctrine of obviousness type double patenting as being unpatentable over the claims of U.S. Patent Nos. 5,843,928; 6,392,071; 6,440,953; 6,482,812; 6,537,981; 6,696,431; 6,774,251; 6,806,262; 6,894,037; 6,992,074; 7,053,075; 7,115,594; 7,208,484; 7,214,670; 6,214,671; 7,232,810; 7,241,747; 7,241,909 and 7,244,719 in view of Bishop et al U.S. 5,972,917 or DeLuca et al WO 96/16035. The Examiner appears to have added an additional obviousness type double patenting rejection based upon U.S. Patent Nos. 6,114,317; 6,566,352; 6,579,861; 6,627,622; 6,887,860; 7,094,774; 7,141,558; 7,241,748 and 7,300,925 in view of Bishop et al (U.S. 5,972,917) or DeLuca et al (WO 96/16035). The Examiner contends that each of these patents teaches 2-alkylidene-19-nor vitamin D compounds useful in treating various diseases such as osteoporosis. Although the Examiner recognizes that the instantly claimed compounds differ from the 2-alkylidene-19-nor vitamin D compounds of the prior art as being 18, 19-dinor derivatives thereof, the Examiner believes that said compounds are obvious over the cited patents. The Applicant disagrees that the presently-claimed compounds are rendered obvious in view of the cited patents for the following reasons.

In the Office action, the Examiner states:

> "First, in order to argue unexpected and/or unobvious results, comparison between the closest prior art compound and the claimed compound is necessary. It is important that said is true side-by-side comparison, i.e., experimentation done under identical conditions. Here, applicant is arguing unexpected/unobvious results based on data from a number of references."

Applicant agrees that an argument relating to unexpected results should compare the closest prior art compound with the claimed compound. However, before turning to such a comparison,

Applicant would like to address the Examiner's statement that the previous comparisons were not "true" side-by-side comparisons, but instead were "based on data from a number of references." The MPEP addresses this issue in §716.02(b) by stating:

> "Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). See *In re Blondel*, 499 F.2d 1311, 1317, 182 USPQ 294, 209 (CCPA 1974) and *In re Fouche*, 439 F.29 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a *prima facie* case of obviousness."

Under the present circumstances, although the data referred to by Applicant is found in a number of different prior art references, all of the data was obtained by the same procedures. For example, cell differentiation data is determined as described by Ostrem et al, J.BIOL.CHEM. 262, 14167-14171, 1987. See for example the present specification at page 36, paragraph 00123. This same technique is utilized to obtain the cell differentiation data in all of the references cited by the Examiner. Likewise, intestinal calcium transport activity is obtained via the everted gut sac technique, as described in paragraph 00135 on page 37 of the present specification. Bone calcium mobilization activity is also determined by the same technique as described in paragraph 00137 on page 38 of the present specification and measured via an atomic absorption spectrophotometer. Thus, the data referred to by Applicant, although set forth in many different references, is obtained via the same techniques. As such, the data would be considered by those skilled in the art to be true comparative data. Although the data was obtained at different times and locations, the data was obtained via the same techniques, and is thus a true comparison of the biological activities of all of these compounds.

With regard to comparing the closest prior art compound with the claimed compound herein, it is noted that the Examiner has not identified what she considers to be the closest prior art compound. However, Applicant believes that prior art compound to be (20S)-2-methylene-19-nor-1α,25-dihydroxyvitamin D_3 (hereinafter referred to as 2MD) with respect to the presently-

claimed compound (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (hereinafter referred to as DP035). The claimed compound DP035 is set forth in claim 12 and illustrated in Formula Ia on page 8 of the application as filed.

With regard to structural differences, the claimed compound DP035 has a hydrogen atom attached at carbon 18 of the molecule. In contrast, the prior art compound 2MD has a methyl group attached at carbon 18 of the molecule. In all other respects, the compounds are identical, and therefore, Applicant believes since this is the only difference between the molecules that the compound 2MD is the closest prior art compound.

Turning now to a comparison of the biological activities of the presently-claimed compound with those of the compound 2MD, the Examiner will see that the compounds have significantly different calcemic activities. With regard to the presently-claimed compound DP035, Applicant refers the Examiner to Figure 4 which illustrates the intestinal calcium transport activity of DP035 and Figures 5 and 6 which illustrate the bone calcium mobilization activity of DP035. In addition, Applicant refers the Examiner to page 6, paragraph 0012 of the present application, as well as page 40, paragraph 00142 for a description of these calcemic activities as they compare to the natural hormone which is 1α,25-dihydroxyvitamin D_3. More specifically, the presently-claimed compound is characterized by having:

> "...relatively high intestinal calcium transport activity, i.e. similar to that of 1α,25-dihydroxyvitamin D_3..." (see paragraph 0012)

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> "...Figure 4 shows that (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) is as active as 1α,25-dihydroxyvitamin D_3 (C001) in intestinal calcium transport activity." (see paragraph 00142)

Thus, it can be concluded that the presently-claimed compound DP035 has intestinal calcium transport activity that is approximately the same as 1α,25-dihydroxyvitamin D_3.

With respect to bone calcium mobilization activity, it is stated that:

> "...while also exhibiting relatively low activity, as compared to 1α,25-dihydroxyvitamin D_3, in their ability to mobilize calcium from bone." (see paragraph 0012)

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> "Also, Figures 5 and 6 show that although (20S)-2-methylene-18,19-dinor-1α,25-dihydroxyvitamin D_3 (DP035) has some ability to mobilize calcium from bone, it is clearly not as active in this regard as 1α,25-dihydroxyvitamin D_3 (C001). Thus, in summary, the (20S)-2-methylene-18,19-dinor analog (DP035) shows a selective activity profile combining high potency in inducing the differentiation of malignant cells, relatively high intestinal calcium transport activity and relatively low bone calcium mobilization activity." (see paragraph 00142)

The calcemic activity of the prior art compound 2MD is set forth in U.S. Patent 5,843,928. In particular, Applicant refers the Examiner to the data set forth in Table 1 at column 16 and the description found at column 15, line 66 through column 16, line 22. More specifically, with regard to intestinal calcium transport activity, the '928 patent states:

> "...To show its selectivity, this compound produced no significant change in intestinal calcium transport at either the 130 or 260 pmol dose, while 1,25-$(OH)_2D_3$ produced the expected elevation of intestinal calcium transport at the only dose tested, i.e. 260 pmol/day."

With regard to bone calcium mobilization activity, the '928 patent states:

> "...When given at 130 pmol/day, its activity on bone calcium mobilization (serum calcium) was of the order of at least 10 and possible 100-1,000 times more than that of the native hormone. Under identical conditions,

> twice the dose of 1,25-$(OH)_2D_3$ gave a serum calcium value of 13.8 mg/100 ml of serum calcium at the 130 pmol dose. When given at 260 pmol/day, it produced the astounding value of 14 mg/100 ml of serum calcium at the expense of bone."

Thus, the compound 2MD disclosed in the '928 patent has extremely high bone calcium mobilization activity, but very little intestinal calcium transport activity. In contrast, the presently-claimed compound DP035 has relatively low bone calcium mobilization activity, but relatively high intestinal calcium transport activity. Thus, the presently-claimed compound has selective activity on intestinal calcium transport, but not on bone, whereas the prior art compound 2MD has selective activity on stimulating bone calcium mobilization, but not on intestinal calcium transport. Thus, the compound DP035 and its closest prior art compound 2MD have directly opposite biological activities.

As a result, the Examiner will see that not only is the presently-claimed compound DP035 structurally different from the prior art compound 2MD, but it has significantly different biological activities. As such, Applicant believes the compound DP035 is not obvious in view of the compound 2MD, and respectfully requests the Examiner withdraw the obviousness type double patenting rejection based upon the compound 2MD.

Applicant would also like to address two other issues presented by the Examiner in the Office Action. First, the Examiner states on page 3 of the Office Action that Applicant has argued that the presently-claimed compound "has little, if any calcemic activity" and as a result would not be useful in treating metabolic bone diseases. Applicant does not believe it has ever argued that the presently-claimed compound DP035 has little, if any, calcemic activity. Applicant has argued that certain prior art compounds having 2-methylene substitutions might have little, if any, calcemic activity, but it has never argued that the presently-claimed compound DP035 has little, if any, calcemic activity. Instead, it is clear from the above comparison set forth in the present remarks that the compound DP035 does have relatively high intestinal calcium transport activity, while also exhibiting relatively low bone calcium mobilization activity. Such calcemic activity could not be characterized as "little, if any, calcemic activity", but instead would be classified as having a selective activity profile combining relatively high

intestinal calcium transport activity and relatively low bone calcium mobilization activity (see paragraph 00142 at page 40 of the specification as filed).

Secondly, the Examiner states on page 4 of the Office Action that the prior art teaches that the introduction of a 2-methylene group affects the biological activity of vitamin D compounds, and specifically states that the introduction of a 2-methylene group "results in compounds with little, if any, calcemic activity." Applicant believes the Examiner incorrectly interprets the prior art. As an example of what Applicant is referring to, the Examiner should review the above comparison of biological activities for the compound DP035 and 2MD. That comparison, and what is disclosed in the '928 patent, clearly indicates that the compound 2MD (which has a 2-methylene group on the A ring) resulted in a compound having bone calcium mobilization activity that was 100 to 1,000 times greater than 1α,25-dihydroxyvitamin D_3. Although Applicant agrees with the Examiner that the substitution of a 2-methylene group would affect the biological activity of a vitamin D compound, Applicant does not agree that such a substitution results in a compound with little, if any, calcemic activity. Clearly, the above summary of the biological activities of 2MD show otherwise. The point Applicant was making in the last response dated August 11, 2008 was that the biological activities of vitamin D compounds are unpredictable, and thus one skilled in the art is not able to predict with any certainty the activity of any particular vitamin D compound until such vitamin D compound is actually tested for such activities. The calcemic activity comparisons set forth in the previous response dated August 11, 2008 of compounds and their 18,19 analogs clearly showed that removing the methyl group at carbon 18 is unpredictable because in each case the 18,19-dinor compounds resulted in compounds having different biological activities from not only the 19-nor compounds from which they were derived, but also from each other.

Finally, the Examiner refers to U.S. Patent No. 6,440,953 as an example of a compound where the introduction of a 2-methylene group resulted in a compound having little, if any, calcemic activity. However, the '953 patent is directed toward homopregnacalciferol compounds, i.e. 2-methylene compounds with a shorted side chain attached at carbon 20. It is believed that the shortened side chain, and not the 2-methylene substitution, is the reason for such compounds having little, if any, calcemic activity because the 25-hydroxyl group is missing in compounds having such a shortened side chain. Applicant believes that it is not the introduction of the 2-

methylene group that results in reduced activity, but it is the shortening of the side chain that results in reduced activity.

In the Office Action, claims 1-17 and 22-71 were also rejected on the ground of non-provisional obviousness type double patenting as being unpatentable over the claims of co-pending application nos. 10/997,698 and 11/351,874 in view of Bishop et al U.S. 5,972,917 or DeLuca et al WO 96/16035. The Examiner appears to have also added an additional provisional obviousness type double patenting rejection based upon the claims of co-pending application nos. 11/697,414; 11/697,434 and 11/697,436 in view of Bishop et al '917 or DeLuca et al '035.

In response, Applicant states that it believes it has addressed the non-provisional obviousness type double patenting rejections based upon the prior art patents via the present response. Thus, if the Examiner agrees with those arguments, and withdraws the double patenting rejections based upon the issued patents cited previously herein, with the result that this provisional obviousness type double patenting rejection is the only remaining rejection, then Applicant requests the Examiner withdraw this provisional rejection so that the present application may proceed to issuance. Reconsideration and withdrawal of this provisional rejection is therefore requested.

An effort has been made to place this application in condition for allowance and such action is earnestly requested.

Respectfully submitted,
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